

**REMARKS**

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1- 4 are in this case. Claims 1-4 have been rejected. Claims 1-3 have now been canceled. Claim 4 has now been amended. New claims 5-22 have now been added.

***Oath or Declaration***

The Examiner points out that the oath or declaration is defective because Inventor Friedman has not initialized and dated changes in residence and post office address. The Examiner further points out that a new Oath or Declaration in compliance with 37 CFR 1.67(a) identifying this application number and filing date is required.

Accordingly, a new Declaration and Power of Attorney are submitted herewith.

***Double Patenting***

The Examiner has rejected claims 1-3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,664,105 B1 (hereinafter 6,664,105). The Examiner points out that although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims 1-3 encompass the antisense oligonucleotide comprising a polynucleotide that targets and inhibits the expression (i.e., mRNA) of the heparanase polynucleotides recited in the 6,664,105 claims. The "sense" nucleic acid molecule sequence is contained in the anti-sense sequence claimed in the 6,664,105 claims.

Claims 1-3 have now been cancelled rendering moot the Examiner's rejection with respect to these claims.

**35 U.S.C. § 112, First Paragraph, Rejections**

The Examiner has rejected claims 1-4 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 1-3 have been now cancelled rendering moot the Examiner's rejection with respect to these claims. Claim 4 has been amended. New claims 5-22 have been added.

The Examiner points out that the specification does not provide adequate written description of the claimed invention. In particular, the instant application claims nucleic acid molecules encoding or capable of hybridizing, to some undisclosed degree, with those nucleic acid molecules encoding heparanases of undisclosed structure.

The Examiner asserts that a generic statement such as nucleic acid molecules encoding or complementary to or hybridizable with "heparanase" or a portion thereof, is not an adequate written description of the genus because it does not distinguish the claimed genus from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. In addition, the Examiner points out that a definition by function (and in the instant case by activity) and wherein the said activity is not correlated with a specific structural feature, does not suffice to define the genus because it is only an indication of what property the heparanase has, rather than what it is. The Examiner further points out that naming a type of material generally known to exist, in the absence of knowledge of what that material consists of, is not a description of that material. The Examiner therefore asserts that one skilled in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant strongly disagrees with the Examiner and wishes to point out that contrary to the Examiner's assertion, the instant application provides sequence and structure/function descriptions of a heparanase molecule in a manner that would enable an ordinary skilled artisan to identify and isolate sequences encoding

heparanase functional homologues and to design and generate PCR primers suitable for amplifying such sequences.

In particular, the instant application discloses the complete sequence of a human heparanase (SEQ ID NO:3) and demonstrates that the heparanase family of sequences is structurally conserved. The conserved nature of heparanases is illustrated by the fact that different heparanase species of human and animal origins, including human platelet heparanase, human malignant tumor heparanases and mouse B16-10 heparanase were capable of reacting with anti-heparanase antibodies raised against a single heparanase species (see page 8 lines 12-27 of the instant application). Similarly, a single pair of oligonucleotide primers (SEQ ID NOs: 6-7) enabled RT-PCR amplification of mRNA transcripts encoding different heparanase species from both malignant and normal cells (see in the Examples section of the instant application). Since immunogenic and RT-PCR reactions are highly specific, the fact that a single antibody can specifically bind several heparanase protein or that a single pair of primers can direct PCR amplification of several distinct heparanase transcripts, clearly indicates that the heparanase genus is structurally conserved as taught by the instant specification. Consequently, the teachings of the instant specification, namely, the sequence set forth by SEQ ID NO: 1 and the primers set forth by SEQ ID Nos: 6 and 7, as well as the descriptions and experimental data indicating sequence conservation between heparanase genes, clearly provide an ordinary skilled artisan with the tools and knowledge necessary for making and using the invention as claimed without having to engage in undue trial and error experimentation and with expectation of success.

An ordinary skilled artisan privileged to the teachings of the present invention will encounter no difficulty in identifying and isolating additional heparanase-encoding sequences from various tissues and species. For example, sequence information of the human heparanase described in the instant application can be utilized for screening genomic databases, such as NCBI GeneBank, for identifying expressed sequences homologous to SEQ ID NO:1. The screening can be effected by a search software such as, for example BLAST<sup>®</sup>. Expressed sequences exhibiting alignment to at least a portion of SEQ ID NO:1 can be considered putative heparanase encoding polynucleotides. Alternatively,

homologous (paralogous or orthologous) heparanase genes can be isolated from various tissues and species by using PCR or RT-PCR techniques which are well known in the art, using the primers set forth in SEQ ID NOs: 6-7 of the instant application.

Isolated putative heparanase genes can be expressed and tested in order to validate heparanase activity using procedures such as those described in the Examples section of the instant application (see, for example, in page 26 line 9 – page 28 line 15; and in page 3 line 8 – page 31 line 15).

Notwithstanding from the above, and in the interest of expediting prosecution in this case, Applicant has elected to amend claim 4 by substituting the function descriptive term “heparanase” with the structure descriptive phrase “a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO:3”. Accordingly, amended claim 4 now recites:

“A pair of oligonucleotides comprising a sense oligonucleotide and an antisense oligonucleotide, being capable of directing PCR amplification resulting in a polynucleotide sequence encoding a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO:3, wherein said polynucleotide sequence is the most prevalent polynucleotide product of said PCR amplification.”.

The heparanase-encoding polynucleotide definition as now recited in amended claim 4 is described in U.S. Pat. No. 5,968,822 to the present inventors (column 12 lines 21-48), which is referenced by the instant application and from which priority is claimed.

Hence, it is the Applicant's opinion that the claimed invention as recited in currently amended claim 4 and new claims 5-22 is described in full, clear, concise, and exact terms that a skilled artisan would recognize the claimed invention.

The Examiner has rejected claims 1-4 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention.

The Examiner points out that the specification does not disclose how to make and/or use the claimed oligonucleotides. The Examiner asserts that the specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass nucleic acid molecules encoding proteins or portions thereof of heparanase of undisclosed structure, or those nucleic acid molecules specifically hybridizable with the heparanase encoding nucleic acid molecules. The Examiner further asserts that there is insufficient disclosure in the specification for the nucleic acid molecules.

As described hereinabove, the polynucleotide sequence of the present invention, as recited in currently amended claim 4 is defined as "encoding at least a portion of a polypeptide sequence at least 90% homologous to at least a portion of SEQ ID NO:3, wherein said polynucleotide sequence is the most prevalent polynucleotide product of said PCR amplification". In addition, the instant application discloses a preferred pair of oligonucleotides being capable of directing PCR amplification of the polynucleotide sequence of the present invention (SEQ ID NOs: 6-7). Since the target polynucleotide sequence for amplification is now structurally defined, alternative pairs of primers capable of directing PCR amplification of the target sequence can be readily constructed using standard methods well known in the art. The use of the primers in directing PCR amplification, such that the polynucleotide sequence of the present invention is the most prevalent polynucleotide product of the amplification, is demonstrated in the examples section of the instant application.

Hence, it is further the Applicant's opinion that the claimed invention as recited in currently amended claim 4 and new claims 5-22 is described in full, clear, concise, and exact terms which enable a skilled artisan to make and use the claimed invention.

### ***35 U.S.C. § 112, Second Paragraph, Rejections***

The Examiner has rejected claims 1-4 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly

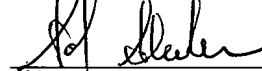
claim the subject matter which Applicant regards as the invention. The Examiners' rejections are respectfully traversed. Claims 1-3 have now been canceled, rendering moot the Examiner's rejection. Claim 4 has now been amended. New claims 5-22 have been added.

The Examiner points out that the recitation of "specifically hybridizable" is indefinite because the specification does not disclose the definition of "specifically hybridizable".

In the interest of expediting prosecution in this case, Applicant has elected to cancel claims 1-3, rendering moot the Examiner's rejection with respect to these claims. In addition, the phrase "specifically hybridizable" has been excluded from currently amended claim 4 and new claims 5-22 to thereby overcome the Examiner's rejection in this case.

In view of the above amendments and remarks it is respectfully submitted that claims 4-22 are now in condition for allowance. Prompt Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,



Sol Sheinbein

Registration No. 25,457

Date: June 23, 2004.

***Encls.***

Combined oath and declaration

Petition for one-month extension fee